Remarks

In accordance with the present invention, there are provided unit dosage forms of cremophor-free nanoparticles of a taxane, associated with a biocompatible polymer (e.g., albumin). Invention unit dosage forms allow systemic administration to a human subject in need thereof at doses and over administration periods and/or treatment cycles not previously possible. Due in part to the ability to deliver taxanes in the form of nanoparticles, and in the absence of cremophor, invention unit dosage forms provide taxanes in amounts which exceed previously accepted levels for maximum dosages. The larger doses of taxanes provided by invention unit dosage forms afford both markedly improved therapeutic benefits and dramatically reduced administration periods, thereby alleviating discomfort experienced by a subject in need of treatment with taxanes.

By the present communication, claims 1, 16, 58, 128 and 145 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as all amended claim language is fully supported throughout the specification and original claims. Claims 4-11, 17-57, 61-73, 79-127, 132-144 and 148-177 were previously canceled. Accordingly, claims 1-3, 12-16, 58-60, 74-78, 128-131 and 145-147 remain pending in this application. A complete set of claims is provided herewith in the Listing of Claims, beginning on page 2 of this communication.

Claim Rejection – 35 U.S.C. § 112

The rejection of claims 1-3, 12-16, 58-60, 74-78, 128-131 and 145-147 under 35 U.S.C. § 112, first paragraph, as allegedly being based on a disclosure which is not enabling is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that "[e]lements which are critical or essential to the practice of the invention, but not included in the claims) are not enabled by the disclosure." See page 2, lines 18-19 of the Office Action. Specifically, Applicants respectfully disagree with the Examiner's assertion that "certain critical elements are not recited in the claims." See page 3, line 5 of the Office Action.

Contrary to the Examiner's assertion, the claims, as amended, are fully enabled by the specification. Indeed, the claims, as amended, fully define the claimed unit dosage forms (and formulations) with respect to both structure and function of the contents of the claimed unit dosage forms (and formulations). Claim 1, for example, specifically contemplates:

a sealed vial containing a sufficient quantity of:

cremophor-free

nanoparticles

of taxane,

associated with a biocompatible polymer,

so as to provide for administration to a human subject of a defined total dose of taxane (e.g., in the range of about 30 mg/m^2 to about 1000 mg/m^2) over a defined administration period (e.g., no greater than about 3 hours) with a defined maximum cycle time between administrations of the total dose (e.g., less than about three weeks).

The remaining claims similarly define the contemplated unit dosage forms and formulations with reference to numerous structural and function features thereof. There are no "critical elements" which are not recited in the claims.

Moreover, support for the preparation of unit dosage forms of cremophor-free nanoparticles of taxanes, associated with a biocompatible polymer, is found throughout the specification. For example, the specification describes cremophor-free taxanes beginning on page 10, and provides exemplary procedures for the preparation of unit dosage forms of cremophor-free taxanes in Example 12 (see, page 41, lines 12-24). Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Double Patenting

The rejections of claims 1-3, 12-16, 58-60, 74-78, 128-131 and 145-147 under the judicially created doctrine of double patenting over (1) claims 1-89 of U.S. Patent No. 6,506,405, and (2) claims 1-14 of U.S. Patent No. 6,753,006, are respectfully traversed. While not

acquiescing to the Examiner's rejection, in order to reduce the issues and expedite prosecution, Applicant submits herewith a terminal disclaimer, disclaiming the portion of any patent to issue on the present application which would extend beyond the term of either U.S. Patent No. 6,506,405 or U.S. Patent No. 6,753,006. Accordingly, reconsideration and withdrawal of these rejections are respectfully requested.

Rejection under 35 U.S.C. § 102(b)

The rejection of claims 1-3, 12-14, 58, 74-76 and 128-129 under 35 U.S.C. § 102(b) as allegedly being anticipated by Sigma Catalog (1992) is respectfully traversed. Applicants' invention, as defined, for example, by amended claim 1, distinguishes over the disclosure of the Sigma Catalog by requiring a unit dosage form comprising a sealed vial containing a quantity of cremophor-free nanoparticles of taxane, associated with a biocompatible polymer, sufficient to provide for administration to a human subject a defined total dose of taxane (e.g., in the range of about 30 mg/m^2 to about 1000 mg/m^2) over a defined administration period (e.g., no greater than about 3 hours), wherein the cycle time between administrations of said total dose is less than about three weeks. The Sigma Catalog does not disclose a unit dosage form containing the materials required by the present claims.

Moreover, Applicants respectfully disagree with the Examiner's assertion that "[t]he only limitation in the claim is the functional limitation." See page 5, lines 5-6 of the Office Action. Contrary to the Examiner's assertion, the claims, as amended, fully define the claimed unit dosage forms (and formulations) with respect to both structure (e.g., cremophor-free nanoparticles of taxane, associated with a biocompatible polymer) and function (e.g., suitable to provide for administration to a human subject a defined total dose of taxane (e.g., in the range of about 30 mg/m^2 to about 1000 mg/m^2) over a defined administration period (e.g., no greater than about 3 hours) with a defined maximum cycle time between administrations of the total dose (e.g., less than about three weeks)) of the contents of the claimed unit dosage forms (and formulations).

Rejections under 35 U.S.C. § 103

The rejection of claims 1-3, 12-14, 58-60, 74-76 and 128-129 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Sigma Catalog cited above, by itself, or in combination with Drug Facts and Comparisons (1994 edition), pages 2780-2785, 3558, is respectfully traversed. Applicants' invention, as defined, for example, by amended claim 1, distinguishes over the cited art by requiring a unit dosage form comprising a sealed vial containing a quantity of cremophor-free nanoparticles of taxane, associated with a biocompatible polymer, sufficient to provide for administration to a human subject a defined total dose of taxane (e.g., in the range of about 30 mg/m^2 to about 1000 mg/m^2) over a defined administration period (e.g., no greater than about 3 hours), wherein the cycle time between administrations of said total dose is less than about three weeks. Neither the Sigma Catalog nor Drug Facts and Comparisons, taken alone or in combination, disclose or suggest a unit dosage form containing the materials required by the present claims.

Moreover, Applicants respectfully disagree with the Examiner's assertion that "[i]t would have been obvious to one of ordinary skill in the art to prepare Taxol formulations without cremophor if this excipient is not suitable for the human condition treated." See page 6, lines 13-15 of the Office Action. Contrary to the Examiner's assertion, cremophor is a commonly used excipient for delivery of insoluble active agents. The use of such excipient, however, limits the dosages of the active agent that can be delivered. The present invention overcomes these limitations and therefore represents a substantial advance in the art.

Furthermore, if the modification suggested by the Examiner was actually obvious, why has the product Taxol been marketed with great success by Bristol Myers Squibb? The answer itself is obvious—because, prior to the present invention, no viable means to deliver the taxane, paclitaxel, absent an excipient such as cremophor, had been developed. The present invention represents a substantial advance in the art by providing alternate means to deliver a taxane (e.g., paclitaxel), without the need for pre-medication, or without the dosage limitations inherent to delivery of cremophor-containing formulations.

Applicants further disagree with the Examiner's assertion that "[o]ne of ordinary skill in the art would be further motivated to use Taxol without cremophor and use in a desired formulation, such Sigma catalog shows the availability of Taxol in pure form without additives." See page 6, lines 8-10 of the Office Action. The availability of a chemical entity (e.g., a taxane such as paclitaxel) from a chemical supplier (Sigma) provides no guidance as to how that chemical entity might be formulated for delivery to a living organism (e.g., human subject). The fact remains that, prior to the present invention, no viable means to deliver a taxane such as paclitaxel, absent an excipient such as cremophor, had been developed. Thus, the Examiner's above-quoted assertion merely reveals the exercise of improper hindsight, having benefit of Applicants' disclosure.

The rejection of claims 1-3, 12-16, 58-60, 74-78, 128-131 and 145-147 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Drug Facts and Comparisons (1994 edition), pages 2780-2785, 3558, or Straubinger, U.S. Patent No. 5,415,869, by themselves or in combination, is respectfully traversed. Applicants' invention, as defined, for example, by amended claim 1, distinguishes over the cited art by requiring a unit dosage form comprising a sealed vial containing a quantity of cremophor-free nanoparticles of taxane, associated with a biocompatible polymer, sufficient to provide for administration to a human subject a defined total dose of taxane (e.g., in the range of about 30 mg/m^2 to about 1000 mg/m^2) over a defined administration period (e.g., no greater than about 3 hours), wherein the cycle time between administrations of said total dose is less than about three weeks. Neither Drug Facts and Comparisons nor Straubinger, taken alone or in combination, disclose or suggest a unit dosage form containing the materials required by the present claims.

As noted above, Applicants again respectfully disagree with the Examiner's assertion that "[i]t would have been obvious to one of ordinary skill in the art to prepare Taxol formulations without cremophor if this excipient is not suitable for the human condition treated." See page 8, lines 1-3 of the Office Action. Contrary to the Examiner's assertion, cremophor is a commonly

used excipient for delivery of insoluble active agents. The use of such excipient, however, limits the dosages of the active agent that can be delivered. The present invention overcomes these limitations and therefore represents a substantial advance in the art.

Furthermore, if the modification suggested by the Examiner was actually obvious, why has the product Taxol been marketed with great success by Bristol Myers Squibb? The answer itself is obvious—because, prior to the present invention, no viable means to deliver a taxane (e.g., paclitaxel), absent an excipient such as cremophor, had been developed. The present invention represents a substantial advance in the art by providing alternate means to deliver a taxane such as paclitaxel, without the need for pre-medication, or without the dosage limitations inherent to delivery of cremophor-containing formulations.

Conclusion

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: February 8, 2005

By: _____

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